

REMARKS/ARGUMENTS

Interview Summary

1. Applicant's attorney gratefully acknowledges the Examiner's courtesy in speaking with the Applicant's attorney, Stephen M. Nipper on May 19, 2006 regarding why the Action was final. In that brief conversation, the Examiner pointed out the previous amendment to the scope of the claims on April 4, 2005.

Amendments in General

2. The specification has been amended by submitting a replacement abstract per the Examiner's request. Such change adds no new matter.

Standards for Patentability

3. "An applicant for a patent is entitled to the patent unless the application fails to meet the requirements established by law. It is the Commissioner's duty (acting through the examining officials) to determine that all requirements of the Patent Act are met. The burden is on the Commissioner to establish that the applicant is not entitled under the law to a patent In rejecting an application, factual determinations by the PTO must be based on a preponderance of the evidence, and legal conclusions must be correct." *In re Oetiker*, 977 F.2d 1443, 1449, 24 USPQ2d 1443, 1447, 24 USPQ2d at 1447 (Fed. Cir. 1992) (Judge Plager concurring).
4. "The precise language of 35 USC 102 that 'a person shall be entitled to a patent unless,' concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under sections 102 and 103." *In re Warner*, 379 F.2d 1011, 1016, 154 USPQ 173 (CCPA 1967), cert. denied, 389 U.S. 1057, reh'g denied, 390 U.S. 1000 (1968).

Claim Rejections - 35 USC § 102

5. The Examiner rejected claims 1-11, 19-20 under §102(b) as being anticipated by Sibalis (USPN 5,328,452).
6. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference."
Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 828 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). MPEP § 2131.
7. Enclosed Table 1 provides a comparison between the basic device taught in USP 5,328,452 (Sibalis) and one embodiment of the present invention.
8. Table 2a is Applicant's summary of the Sibalis device. Table 2b is Applicant's summary of one embodiment of the present invention.

9. Referring initially to Table 1, with respect to Sibalis the symbols therein shown have the following meanings:

S = source
V = voltmeter
A = amperometer
K = switch
E = electrode
CSI = intermediate exit circuit
CS = true exit circuit
Rh = rheostate
TB = biological tissues

10. Turning now to the schematic representation of the device of the present application the symbols therein shown indicate:

S = source
TB = biological tissue
E = electrode

11. Turning now to Table 2a and the cited portion of Sibalis, it is readily appreciated that in Sibalis the two electrodes (20 and 30) are alike, because both allow the passage of current. The two electrodes (20 and 30) are positioned on the same surface to be treated. They are characterized by the fact that one of them is negative (whereby a positive electrical field is generated) and the other one is positive (thus leading to a negative electrical field). These electrodes are used with reference to the ionic properties of the drugs or substances, but only few substances are ionisable.

12. In summary, the system of Sibalis is a system of ionic conductivity (ionophoresis – ionic transport). In Sibalis, the closing of the circuit takes place through the skin, namely through the only one biological resistance because it is not supplied with blood.

13. Before specifying the differences between the present invention and Sibalis, it seems worth to reflect the main features of one of the embodiments of the present invention.

14. The apparatus used in this embodiment of the present invention comprises a modulator of electrical current, by which electric pulses are sent to the circuit, and a circuit consisting of two terminals, one of which comprises a container for the substance as a solution to be transdermally transferred provided with a dispensing electrode at the top and the other one is a rubber plate by which, upon being positioned on the skin surface, the circuit is closed.

15. Additionally, the apparatus comprises a microprocessing unit together with a keyboard for programming the desired treatment, a graphic display by which each operation is visually shown, as well as electronic control devices for the correct connection of the cables to each exit.

16. The treatment carried out with the apparatus comprises using an iterative current, consisting of a succession of stimuli separated by stop times, which are repeated a number of times at a frequency which can be modulated. The applied current is pulsed, of triangular shape and monodirectional, consisting of a wave train with sinusoidal behaviour.

17. As a consequence, the molecules of the substance to be transferred may pass through the skin barrier with a simultaneous balancing of counterions.

18. Owing to the potential difference applied to the skin which has a negative charge, at the skin a motion of undissociated molecules takes place.

19. In this way also, the transdermal transfer of neutral molecules is allowed, according to the formula $F = ZDI/4hk$, wherein F is the electroosmotic flow, Z is the double layer potential, D is the dielectric constant, I is the current (as amperes), k is the conductivity (as ohm) and h is the viscosity coefficient.

20. Each molecule, owing to the potential difference, has a more or less speedy movement according to the formula $M.el. = ZD/4k$, wherein $M.el.$ is the electrophoretic mobility.

21. Moreover, the pressure applied by the dispensing roller causes the transfer of the drug or substance to be further enhanced owing to the so-called streaming potential.

22. All these physical processes, by influencing the capacity of the biological membranes of being polarized, cause the channels within which the molecules of interest enter to be activated.

23. In all living organisms consisting of cells encompassed by membranes, the ionic channels act as gates between the intracellular and extracellular space, these gates opening and closing to permit the passage of molecules of several sizes and positively or negatively charged in order to maintain the cell balanced with the surrounding environment.

24. These molecules open and close (gating) as a consequence either of the bonding with a specific ligand or of a particular change of electrical voltage. The selectivity of all ionic channels seems to be based on a common mechanism: ions coordinated by partial

charges generate an electrostatic environment which attracts the ions without a very strong bonding, whereby the efficiency of the flow is not reduced.

25. Nowadays (thanks to the contribution of the Nobel prize Peter Agre of the John Hopkins University) it is known that a special permit controls the entry of the molecules through the specifically selective filter (namely the membrane ionic channel), this permit consisting of proteins forming the cellular membrane representing the last control (namely, the gating (i.e., the opening and closing of the molecules)) and acting as a gate to keep the cell balanced with the environment.

26. In order to attract the "suitable ions," the cell generates inside the channel a structure like that of the molecule containing a determined ion in the outer environment.

27. The apparatus, thanks to the choice of the described electrical frequencies, creates the conditions suitable for said gating whereby each cell may open and close the channel according to different needs.

28. In the present invention, the ionic channels of the cells of the tissue in the need of the substance to be administered are activated so as to receive both ions and neutral molecules.

29. Consequently, in the present invention the substance or drug to be administered is not fed to the blood circuit, is instead supplied directly to the tissue in the need thereof by trespassing the skin up to 10 centimeters of deepness.

30. Otherwise stated, the substance or drug to be administered passes through the several layers forming the skin without lesion thereof and without involving the circulation system.

31. In this way, the substance or drug is brought directly to the place where it must act without incurring any modification due to metabolic mechanisms as it happens with the other administration routes.

32. Consequently, in the present invention only one electrode permits the administration of the substance or drug as a liquid solution the other electrode being applied to the skin as a plate of conductive rubber and serving only for the closing of the electrical circuit.

33. There is no possibility of inverting the role of the electrodes as it is possible with Sibalís. More specifically, by referring to Sibalís claim 1:

(a) it relates to a *"transdermal applicator for delivering at least one drug through the skin to the blood circulation system of a patient over an extended period of time comprising...."*. As already stated, the present invention, as confirmed by the experimental tests reported in the specification, is not at all looking to the transfer of the substance being transferred (drug) to the haematic circle under the skin.

(b) Sibalís (claim 1) provides *"a drug reservoir for containing at least one drug for attachment to the skin of a patient and making an electrical connection therewith at an interface between the reservoir and the skin of the patient"*. The present invention on the contrary does not provide a direct contact between the electrode and all the substance to be transferred, whereas in Sibalís there are set the direction of the electrical current, the amplifying of the conductive surface, and the whole

content of the reservoir 12 containing the substance to be administered is electrically charged and an interface 14 is thus created, which is a resistance surface.

- (c) Looking at the paragraph of the claim 1 of Sibalis reading "*...means connected to said reservoir including a source...(omissis).....to develop and maintain current flow including current flow within blood capillaries of the patient in a desired same direction of current flow*".

34. For these reasons, Sibalis does not anticipate the claims of the present invention.

Conclusion

If the Examiner feels it would advance the application to allowance or final rejection, the Examiner is invited to telephone the undersigned at the number given below.

Reconsideration and allowance of the application as amended is respectfully requested.

DATED this 3rd day of August, 2006.



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